Original Article

Risk predictors for the development of retinopathy of prematurity in very low birth weight neonates

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Received – 14 July 2016 Initial Review – 19 August 2016 Published Online – 09 November 2016

ABSTRACT

Background: Retinopathy of prematurity (ROP) is an important cause of visual and neurological impairment in premature infants. Identification of risk factors and effective management of the same will help in better outcomes. Information on ROP and its risk factors are limited especially from South India and interventions directed at prevention and treatments have produced only modest results. **Methods:** The study was of a prospective, unmatched case–control design and was conducted in premature, very low birth weight infants (<34 weeks; <1500 g) admitted to Neonatal Intensive Care Unit in a tertiary care center in South India during an 18-month period. The neonates were screened for ROP and subjects who developed ROP were classified as cases and those who did not were categorized as controls. The maternal risk factors studied were the type of delivery, maternal fever, pregnancy-induced hypertension (PIH), gestational diabetes mellitus, cardiac disease, premature rupture of membrane, antepartum hemorrhage, chorioamnionitis, multiple pregnancy, infertility treatment, urinary tract infections, polyhydramnios, and oligohydramnios. The neonatal factors studied were gestational age, birth weight, septicemia, apnea, anemia, hypotension, need for inotropic support, type and duration of oxygen therapy, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, and phototherapy. Both univariate and multivariate analyses were carried out. **Results:** A total of 54 cases and 54 controls (1:1) were enrolled into the study. Males dominated the study (63% of cases). Univariate analysis showed gestational age, PIH, birth weight, sepsis, oxygen administration, hypotension and packed cell transfusion as important risk factors for ROP. On binary logistic regression analysis, birth weight (odds ratio: 6.00; p: 0.014), oxygen exposure (odds ratio: 11.05; p: 0.003), and hypotension (odds ratio: 6.85; p: 0.009) were identified as important risk predictors of ROP. **Conclusions:** The study adds important information to the understanding of risk factors of ROP.

Key words: *Retinopathy of prematurity, Risk predictors, Very low birth weight infants*

Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative disorder of the retina and was first described by Terry in 1942 [1,2]. Approximately, 65% of infants with birth weight <1250 g and 80% of those with birth weight <1000 g develop some degree of ROP [3,4]. The incidence of ROP in the Indian population has been estimated to be up to 46% and is on the rise in this part of Asia due to increasing incidence of preterm deliveries [5-7]. Due to wide variability among populations, studies have provided only incomplete results [8,9]. Identifying risk factors for ROP will help to initiate corrective measures in a neonate at potential risk for developing ROP and hence the rationale behind the study.

METHODS

The study aimed to evaluate the risk factors for the development of ROP in preterm very low birth weight neonates. The study was a prospective, unmatched case–control study conducted in a tertiary care center in Kerala, India that was commenced after obtaining approval from the Institutional Ethics Committee.

The study was conducted in subjects admitted to the Neonatal Intensive Care Unit (NICU) after obtaining written informed consent from the parents. The inclusion criteria consisted of preterm babies (gestational age <34 weeks) weighing <1500 g who developed ROP of any severity. Neonates with congenital anomalies and those who did not satisfy the inclusion criteria were excluded from the study. Controls were defined as preterm babies (<34 weeks gestational age) weighing <1500 g admitted to NICU and who did not develop ROP.

The study was conducted for 18 months, and various risk factors for the development of ROP were analyzed. The maternal factors studied were the type of delivery, maternal fever, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), cardiac disease, premature rupture of membrane (PROM), antepartum hemorrhage, chorioamnionitis, multiple pregnancy, infertility treatment, urinary tract infections (UTI),

polyhydramnios, and oligohydramnios. The neonatal factors studied were gestational age, birth weight, septicemia, apnea, anemia, hypotension, need for inotropic support, type and duration of oxygen therapy, patent ductus arteriosus (PDA), necrotizing enterocolitis, intraventricular hemorrhage, and phototherapy. All the relevant clinical and biochemical data required for the study were obtained.

Birth asphyxia defined by WHO as failure to initiate and maintain spontaneous respiration was determined using the APGAR score. Apnea was defined as cessation of respiration for >20 s or cessation of respiration of any duration accompanied by bradycardia (heart rate <100/min) and/or cyanosis. Sepsis was diagnosed clinically by common signs such as hyperthermia or hypothermia, respiratory distress, apnea, cyanosis, jaundice, hepatomegaly, abdominal distension, feeding abnormalities, and neurological abnormalities like seizures. The same was supported by laboratory evidence such as micro erythrocyte sedimentation rate, C-reactive protein, absolute neutrophil count and blood culture, urine culture, and cerebrospinal fluid analysis. PDA was diagnosed clinically and by echocardiography. Intraventricular hemorrhage was diagnosed by cranial ultrasonography. Hypotension was defined by a combination of criteria defined as mean blood pressure less than gestational age in weeks with evidence of poor systemic perfusion defined as a prolonged capillary refill time >3 s [10,11]. Hyperbilirubinemia and hours of phototherapy and units of packed red blood cell transfusion were noted. Details of oxygen administration, duration, and mode of oxygen administration were also recorded.

All the preterm babies who were admitted to the NICU satisfying the study criteria were referred to the Department of Ophthalmology in the same institute at 4 weeks of postnatal age. Screening for ROP was done by an experienced ophthalmologist. The eye was dilated using 1% tropicamide and 2.5% phenylephrine drops. After half an hour, the eye was examined with indirect ophthalmoscope with a 20–diopter lens. No local anesthesia was used during the procedure. ROP was classified, according to the international classification of ROP criteria, location as zone 1, 2, 3 extended in clock hours and severity as Stage 1, 2, 3, 4 and 5. Threshold stage ROP/pre-threshold ROP was also noted.

Stages 1 and 2 ROP were usually followed every week/2 weeks until resolution or progression to more advanced stage. Stages 3, 4 and 5 ROP were treated by/advised intervention such as laser/surgery. Cryotherapy and diode laser therapy were the usual mode of treatment for threshold ROP and those requiring interventions were referred to higher center for further management. Those without ROP were re-examined every 2 weeks. Furthermore, Stages 1 and 2 were followed weekly and more frequently in those with ROP stage 3 and above. Babies were then reviewed in the newborn follow-up clinic.

Statistical Analysis

Based on a previous study, the odds ratio of low gestational age for the development of ROP in the premature babies was 3.1 [12]. The sample size thus calculated based on the study was 108 with 54 cases and 54 controls (1:1). The quantitative variables under the study were described by mean with its 95% confidence intervals (CIs) and qualitative variables with frequencies and proportions. Chi-square test was used in case of categorical variables. Binary logistic regression was used to find out independent predictors of the outcome. The odds ratio with its CI given by the model was taken as the strength of association in the final analysis. The analysis was done using SPSS software in coordination with the Department of Community Medicine of the same institute.

RESULTS

A total of 108 cases were enrolled with cases and controls in a ratio of 1:1. Fig. 1 shows the study disposition, and Table 1 shows the various baseline demographic and clinical characteristics. Male subjects predominated the study. The majority of the cases as well as controls had a birth weight <1200 g. All the subjects in the study population had a gestational age between 28 and 34 weeks. Various risk factors in mother and baby were studied for the strength of association with ROP. None of the mothers had maternal fever, chorioamnionitis, or polyhydramnios. The various modes and duration of oxygen administration and its association with ROP were also studied (Fig. 2 and Table 2).

Univariate analysis revealed gestational age, PIH, birth weight, sepsis, oxygen administration, hypotension, and packed cell transfusion as important risk factors for ROP. On multivariate binary logistic regression, birth weight (odds ratio: 6.00; p: 0.014), oxygen exposure (odds ratio: 11.05; p: 0.003), and hypotension (odds ratio: 6.85; p: 0.009) were identified as important risk predictors of ROP (Table 3). Approximately one-quarter of neonates (Table 1) affected with ROP required intervention and were referred to higher center for the same.

DISCUSSION

ROP has been found to be an important cause of childhood visual impairment and blindness and affects the normal motor, language and social development of the child. Retinal vascularization starts at around 15th week of gestation and is completed by around 36 weeks in the nasal side and by term in the larger temporal side [13]. Central to the pathogenesis of ROP is interference with the normal maturation of the retina secondary to factors such as hyperoxia and angiogenic factors like vascular endothelial growth factor.

ROP incidence is inversely related to birth weight and gestational age, and studies have shown that 80% of infants with birth weight <1000 g show some evidence of ROP [14,15]. Similar findings were replicated in our study also where 90.7% of babies with birth weight of <1200 g developed ROP. Although decreasing birth weight has been associated with both incidence and severity of ROP, decreasing gestational age is only associated with incidence of ROP. No major studies till date have proven to have a gender preference with the occurrence of ROP. Our study showed that the incidence of ROP was more in male infants, but was not significant (p=0.243).

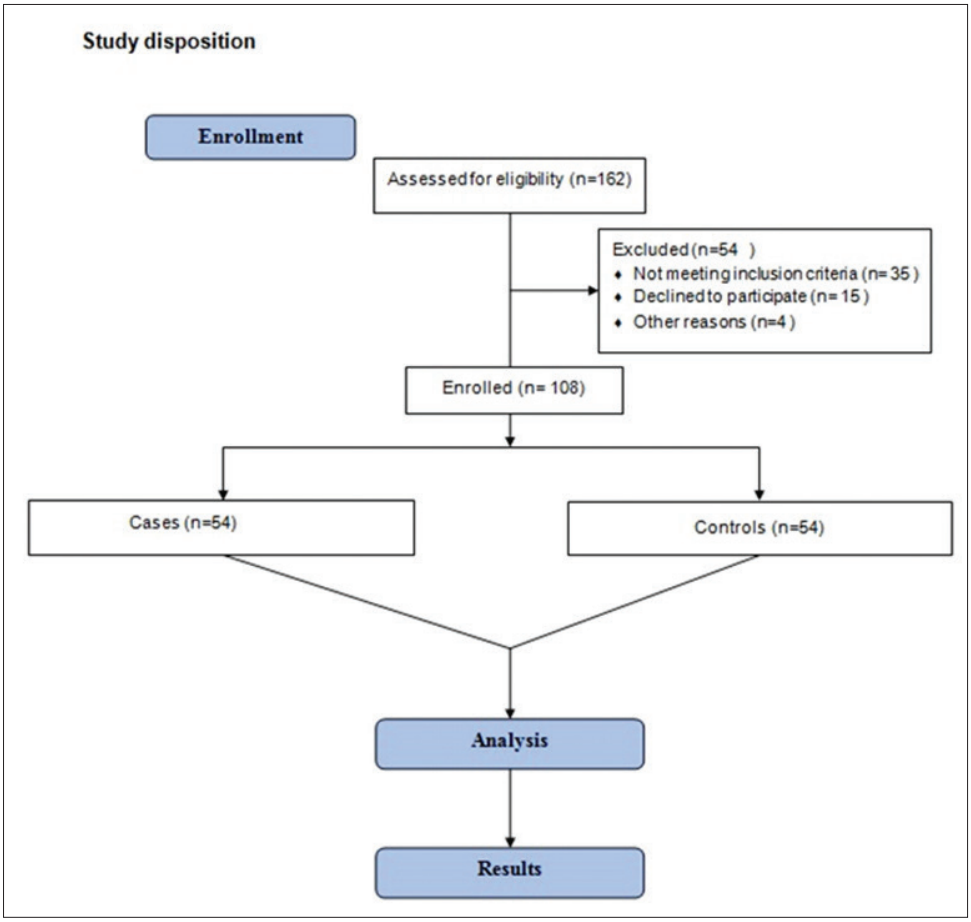

Figure 1: Study disposition

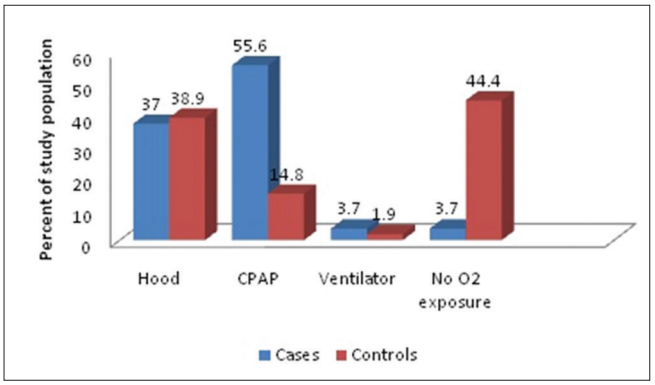

Figure 2: Modes of oxygen exposure: Percentages in the study population

Maternal factors play a major part in determining pregnancy outcomes, and hence, were studied for association with incidence of ROP. Several putative factors such as type of delivery, maternal fever, PIH, GDM, UTI, cardiac disease, PROM, chorioamnionitis, antepartum hemorrhage, multiple pregnancy, infertility treatment, polyhydramnios, and oligohydramnios were considered. Although PIH was found to have a positive association with the development of ROP in univariate analysis (Table 1; p=0.008), multivariate analysis failed to prove the same (Table 3; p=0.157). Maternal pre-eclampsia has been found to have a protective effect against development of ROP in various studies. Hypertension causes intrauterine stress and subsequent maturation of the eyes. Treatment for infertility, PROM, GDM, and mode of delivery were not found to be associated with the development of ROP in this study. However, studies have proven otherwise also [16]. Of late, babies conceived via in vitro fertilization have been found to have an increased incidence of ROP, probably due to the higher incidence of preterm delivery and multiple pregnancies associated with the same.

Just like the maternal factors and even more important in the pathogenesis of ROP is the role played by neonatal factors. It is very well proven that high inspired oxygen is an important risk factor for ROP [17,18] and strict control of oxygen exposure during the neonatal period is associated with lower incidence of ROP [19-23]. In our study, it was noted that 96.3% of the cases had been exposed to oxygen as compared to 55.6% of the controls ([p=0.000]; odds ratio=20.8 [95% CI 4.59-94.24]). Several theories such as free radical injury, stimulation of vasogenic factors, and physiologic differences between choroidal and retinal circulations have been hypothesized for the development of ROP in those with increased oxygen exposure. Both the mode and duration of oxygen administration were also taken into consideration (Table 2).

Of the various other risk factors, sepsis [24], hypotension [25], and blood transfusion [26,27] were found to have significant association with the occurrence of ROP (Table 1). The hypothesized reason for the higher rates of ROP in these settings has been inflammation and subsequent free radical injury associated

Table 1: Baseline characteristics of the study population

Variable	Cases (n=54) (%)	Severe ROP cases: Stage III and above (n=13)	Controls (n=54) (%)	p value* (total cases versus controls)
Sex				
Male	63	72	52	0.243
Female	37	28	48	
ROP stages				
I	54	-	-	-
II	22	-	-	-
III	18.5	-	-	-
IV	5.5	-	-	-
V	-	-	-	-
Maternal risk factors				
Vaginal delivery	63	62	72	0.270
Gestational age				
28-32 weeks	51.9	76	29.6	0.001
32-34 weeks	48.1	24	70.4	
PIH	16.7	25	1.9	0.008
PROM	40.7	42	24.1	0.064
GDM	33.3	31	25.9	0.399
Infertility treatment	11.1	20	7.4	0.507
Neonatal risk factors				
Birth weight≤1200 g	90.7	92	70.4	0.007
1201-1500 g	9.3	8	29.6	
Septicemia	33.3	40	16.7	0.046
Hypotension	42.6	60	5.6	0.000
Packed cell transfusion	25.9	33	7.4	0.010
Oxygen administration	96.3	100	55.6	0.000
Apnea	27.8	40	16.7	0.165
Birth asphyxia	16.7	25	11.1	0.404
NEC	16.7	14	5.6	0.066
Phototherapy	40.7	50	48.1	0.439

ROP: Retinopathy of prematurity, PIH: Pregnancy induced hypertension, PROM: Premature rupture of membrane, GDM: Gestational diabetes mellitus, NEC: Necrotizing enterocolitis, *p<0.05

Table 2: Duration of oxygen administration

O_2 duration	Cases (%)	Control (%)	Total (%)
>6 days	30 (55.6)	5 (9.3)	35 (32.4)
4-6 days	17 (31.5)	9 (16.7)	26 (24.1)
1-3 days	5 (9.3)	16 (29.6)	21 (19.4)
None	2 (3.7)	24 (44.4)	26 (24.1)

Table 3: Multivariate logistic binary regression analysis

Factor	Adjusted odds ratio (95% CI)	p value
Birth weight	6.00 (1.44-24.97)	0.014
O_2 administration	11.05 (2.28-53.66)	0.003
Sepsis	1.49 (0.45-4.92)	0.521
Hypotension	6.85 (1.62-29.01)	0.009
Blood transfusion	2.029 (0.49-8.37)	0.328
Maternal PIH	5.633 (0.52-61.59)	0.157

PIH: Pregnancy induced hypertension, CI: Confidence interval, *p<0.05

with the same. The association of PDA, apnea, phototherapy and hyperbilirubinemia with the incidence of ROP could not be proven in our study and warrants further research [28-31]. In our study, the factors which were found to be significant on univariate analysis were maternal PIH, birth weight, gestational age, oxygen administration, blood transfusion, hypotension, and systemic infection. The factors found to be significant on univariate analysis were subjected to a multivariate analysis using binary logistic regression analysis. A model was constructed in which 37.8% of the factors contributing to the occurrence of ROP could be predicted. Gestational age had strong correlation with birth weight (correlation coefficient = 1) and hence was omitted from the model. Birth weight, oxygen exposure, and hypotension were found to be significant risk predictors of ROP (Table 3).

Nearly a quarter of neonates affected with ROP needed interventions due to their advanced stage. The prevalence of most of the risk factors in those with severe stages of ROP (stage III and above) were found to be significantly higher than those with lesser stages (Table 1). They were referred to higher tertiary care institute for further management and follow-up. Judicious use of oxygen and blood products in premature low birth weight

neonates, optimal management of blood pressure, and institution of neonatal screening programs for ROP will all do a lot in the long run and help in improving outcomes.

There were certain limitations in our study. The study design - unmatched case–control type - by itself has its own limitations. Genetic factors were not taken into consideration due to lack of infrastructure for the same. Larger studies in similar populations are needed to validate the findings of this study and delineate the intricacies of the disease further. Since it was mainly a cross-sectional data analysis, long-term follow-up was not performed. Similarly, follow-up of infants referred for interventions could not be performed due to technical limitations.

CONCLUSIONS

In the present era of advanced neonatal care and management where the incidence of ROP is on the rise, identifying risk predictors helps in better understanding of the disease. Although active interventions toward the same have not yielded promising results still search is on to tackle the menace of ROP that is on the rise. This study has identified birth weight, oxygen administration and low blood pressure as major predictors of ROP and adds important information to the present day knowledge of ROP.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Shreetal S, Sobhakumar S, Rhiju R, Nair SR. Risk predictors for the development of retinopathy of prematurity in very low birth weight neonates. Indian J Child Health. 2017; 4(1):22-26.